

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :

A61K 9/22, 9/52

A2

(11) International Publication Number:

WO 97/37640

(43) International Publication Date:

16 October 1997 (16.10.97)

(21) International Application Number:

PCT/US97/04495

(22) International Filing Date:

20 March 1997 (20.03.97)

(30) Priority Data:

60/014,889

5 April 1996 (05.04.96)

US

(71) Applicant (for all designated States except US): ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): AYER, Atul, Devdatt [US/US]; 931 Bautista Court, Palo Alto, CA 94303 (US). LAM, Andrew [US/US]; 1506 38th Avenue, San Francisco, CA 94122 (US). MAGRUDER, Judy, A. [US/US]; 1233 Wasatch Drive, Mountain View, CA 94040 (US). HAMEL, Lawrence, G. [US/US]; 1215 Arbor Court, Mountain View, CA 94040 (US). WONG, Patrick, S.-L. [US/US]; 2030 Cornell Street, Palo Alto, CA 94306 (US).

(74) Agents: SABATINE, Paul, L. et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).

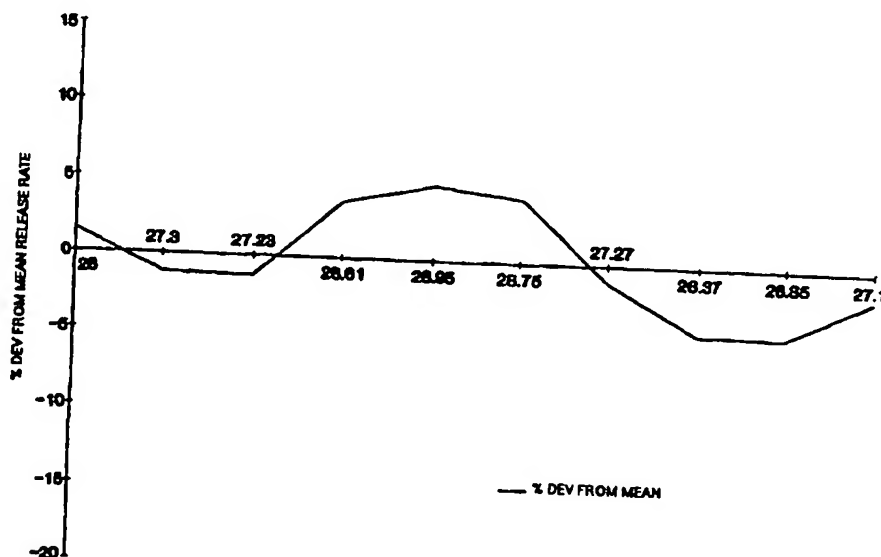
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

BEST AVAILABLE COPY

(54) Title: UNIFORM DRUG DELIVERY THERAPY



(57) Abstract

The invention disclosed pertains to a novel delivery system comprising an agent formulation and means for dispensing the agent formulation from the delivery system.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LJ	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

UNIFORM DRUG DELIVERY THERAPY

FIELD OF THE INVENTION

This invention pertains to a dosage form that provides a substantially uniform delivery of drug over an extended period of time. More particularly, the invention concerns a dosage form that provides a known and constant drug release pattern for an indicated therapy. The invention relates also to a dosage form that provides a controlled-constant and uniform delivery of a known dose of drug over time.

BACKGROUND OF THE INVENTION

A critical need exists for a dosage form for the controlled and uniform administration of a drug for therapy over time. Presently, in the practice of pharmacy and medicine, a drug is administered in conventional pharmaceutical forms, such as tablets and capsules. These conventional forms deliver their drug by dumping and this leads to uneven dosing of drug, to uneven blood levels of drug characterized by peaks and valleys, and accordingly this does not provide controlled and uniform therapy over time.

The prior art provided dosage forms for continuous therapy. For example, in United States Pat. No. 4,327,725 issued to Cortese and Theeuwes, and in United States Pat. Nos. 4,612,008; 4,765,989; and 4,783,337 issued to Wong, Barclay, Deters and Theeuwes, a dosage form is disclosed that provides therapy by generating an osmotic pressure inside the dosage form. The dosage form of these patents operate successfully for delivering a drug for a preselected therapy. With the delivery of some drugs however, these dosage forms often exhibit erratic release rate patterns, such as a nonuniform variation in the drug release rate, and the dosage form can stop delivering a drug, that is, the dosage form can shut-down intermittently.

1 It is immediately apparent, in view of the above presentation, that an
2 urgent need exists for a reliable dosage form. The need exists for a dosage
3 form endowed with properties for delivering a drug at a substantial and
4 uniform rate over time. The need exists also for a dosage form substantially
5 free-of-deviation in its release-rate profile, that delivers the needed dose of
6 drug with a reduced amount of drug left in the dosage form at the end of the
7 delivery period. It will be appreciated by those knowledgeable in the drug
8 dispensing art, that is novel and unexpected dosage form is made available
9 that provides a substantially uniform and known drug-release profile, free of
10 the tribulations of the prior art, such a dosage form would represent an
11 advancement and a valuable contribution in the drug dispensing art.

12 13 OBJECTS OF THE INVENTION

14
15 Accordingly, in view of the above presentation, it is an immediate
16 object of the invention to provide a dosage form that delivers a drug in a
17 substantially uniform dose to a biological drug receiving environment over
18 an extended drug-delivery therapy time.

19 Another object of the invention is to provide a novel dosage form that
20 substantially avoids administering a drug in a nonuniform and varying rate
21 and therefore exhibits substantially the same dose-dispensing rate over time.

22 Another object of the invention is to provide a dosage form that
23 delivers a predetermined and prescribed dose in the same manner over time
24 while simultaneously lessen the amount retained or the residual drug left in
25 and not delivered from the dosage form.

26 Another object of the invention is to provide a drug composition of
27 matter comprising drug particles of 5 μm to 150 μm , micron, and hydrophilic
28 polymer particles of 5 μm to 250 μm , characterized by the drug particles and
29 the hydrophilic polymer particles functioning together to provide a uniform

1 and nonvarying rate of release of both substantially-free of a deviation and
2 substantially-free of a decrease in the rate of the release over time.

3 Another object of the invention is to provide a dosage form comprising
4 a membrane that surrounds a drug core comprising drug particles of 1 to
5 150 μm and hydrophilic polymer particles of 1 to 250 μm , particles which
6 are co-delivered from the dosage form through an exit formed by a process
7 selected from the group consisting of a drilled exit, a bioerosion exit,
8 a leaching exit, a solubilizing exit, and an exit formed by rupture.

9 Another object of the invention is to provide a dosage form comprising
10 a membrane comprising a semipermeable composition that surrounds a core
11 comprising a drug layer comprising drug particles of 1 to 150 μm and polymer
12 particles of 1 to 250 μm , and a displacement layer comprising an
13 osmopolymer-hydrogel that imbibes fluid, hydrates and increases in swelling
14 volume and thereby displaces the drug layer through an exit membrane
15 selected from an exit in the group consisting of an orifice, passageway, pore,
16 microporous channel, porous overlay, porous insert, micropore, microporous
17 membrane and porepassageway.

18 Another object of the invention is to make available a process for
19 providing a substantially uniform and substantially nonvarying drug delivery
20 program from a dosage form, wherein the process comprises the steps of
21 selecting drug particles of 1 to 150 μm , selecting hydrophilic polymer particles
22 of 1 to 250 μm , blending the selected particles into a drug-polymer core, and
23 surrounding the core with a membrane comprising means for delivering the
24 drug from the core in a substantially-uniform and substantially-nonvarying rate
25 of release over a period of time up to 30 hours.

26 Another object of the invention is to provide a dosage form for
27 delivering a drug to human, wherein the dosage form comprises a drug
28 composition comprising 0.05 ng to 1.2g of drug having a particle size of
29 1 to 150 μm , and a hydrophilic polymer having a particle size of 1 to 250 μm ,
30 a push composition that imbibes fluid and expands for pushing the drug

1 composition from the dosage form, a wall that surrounds the drug and the
2 push composition and is permeable to the passage of fluid, an inner coat that
3 surrounds the drug and push compositions positioned between the inside
4 surface of the wall and the drug and push compositions for governing fluid
5 imbibition into the drug and push compositions for 30 minutes to 4 hours and
6 30 minutes, and at least one exit means in the wall for delivering the drug
7 composition at a uniform and nonvarying rate over time.

8 Other objects, features, and advantages of the invention will be more
9 apparent to those versed in the dispensing art comprising medicine and
10 pharmacy from the following detailed specification taken in conjunction with
11 the accompanying claims.

12 13 BRIEF DESCRIPTION OF THE FIGURES 14

15 Figure 1 illustrates the drug release rate variation with a drug
16 possessing a particle size of 2 to 900 microns in the presence of a polymer
17 possessing 25% and more of greater than 250 micron size.

18 Figure 2 illustrates the drug release rate variation from a dosage
19 form with a drug size of less than 150 micron in the presence of a polymer
20 possessing 25% and more of greater than 250 micron.

21 Figure 3 illustrates pronounced decrease in the variation of the
22 drug release rate when the dosage form comprises a drug size of less than
23 150 micron accompanied by a polymer size of less than 250 micron.

24 25 DESCRIPTION OF THE INVENTION 26

27 The following examples are illustrative of the invention and they
28 should not be considered as limiting the invention in any way, as these
29 examples and other equivalents thereof will become apparent to those

1 versed in the dispensing art in the light of the present specification and
2 the accompanying claims.

3
4 EXAMPLE 1
5

6 A dosage form for delivering a drug orally to the gastrointestinal tract of
7 the drug receiving patient in need of the drug's therapy is prepared as follows:
8 first 5 mg of 135 μ m amlodipine besylate, a calcium channel blocker, is
9 blended with a 5% solution of poly(vinylpyrrolidone) of 30,000 number
10 average molecular weight available from General Aniline and Film
11 Corporation, New York, New York, in a fluid bed processor. Then, the
12 granulated product is combined with 7.5 mg of 235 μ m a poly (alkylene
13 oxide), a poly(ethylene oxide), of 175,000 number average molecular weight
14 available from the Union Carbide Corporation, Danbury, Connecticut, 0.5 mg
15 of sodium chloride and 0.02 mg a stearic acid, and blended to provide a
16 homogenous blend, by blending 35 rpm for 7 minutes. The homogenous
17 blend is compressed into a drug composition and surrounded with a wall
18 comprising a semipermeable composition and an exit forming agent.

19 The wall composition comprises 65 wt% cellulose acetate having an
20 acetyl content of 34% and a 30,000 number average molecular weight
21 dissolved in acetone:water, to which 1.8 wt% triacetin and 1.5 wt% sodium
22 chloride are added with stirring constantly. The drug composition is sprayed
23 in a fluidized bed air suspension coater to provide 10% wt wall. The dosage
24 form is dried at 25°C for 18 hours. The dosage form releases the amlodipine
25 besylate in a nonvarying rate through microchannels formed by fluid leaching
26 of the sodium chloride in the gastrointestinal fluid of the patient.

EXAMPLE 2

The procedure of the above example is followed in this example, wherein in the present example the drug is selected from the group consisting of 5 mg of lisinopril indicated as an angiotensin converting enzyme inhibitor, 10 mg of buspirone hydrochloride indicated as an antianxiety drug, and 5 mg of oxybutynin hydrochloride indicated for relief of bladder instability, and wherein the lubricant is magnesium stearate and the semipermeable wall comprises mannitol.

EXAMPLE 3

A dosage form for the osmotically and hydrokinetically controlled release of a beneficial drug is made as follows: first, to a mixing bowl is added 500 mg of the oral antibacterial ciprofloxacin hydrochloride of 125 microparticle size followed by the addition of 105 mg of sodium carboxymethylcellulose of 22,000 number average molecular weight of 135 micron sizes and the ingredients mixed for 3 to 5 minutes to yield a homogenous mix. Next, 10 mg of 88 microcrystalline cellulose of 11,000 number average molecular weight is added to the mixing bowl and 0.05 mg of drug delivery surfactant sodium lauryl sulfate added to the bowl and all the ingredients mixed for 5 minutes. Then, an aqueous solution containing 7.5 mg of poly(vinylpyrrolidone) of 30,000 number average molecular weight is added with mixing and the resulting mixture is passed through an extruder onto a small tray and let dry overnight. The granulation is dried for 5 hours at 50°C and 0.03 mg of lubricant added with mixing for 1 minute. A solid fluid imbining osmotic core is prepared in tablet press with a concave punch.

Next, an internal subcoat, drug free, is prepared comprising 94 wt% hydroxyethylcellulose of 90,000 number average molecular weight and 6 wt% polyethylene glycol in distilled water is coated around the drug composition

1 and the subcoated drug composition is dried for 1 hour at 45°C. Then, an
2 outer coat comprising a semipermeable composition and a pore-passageway
3 former is prepared by adding cellulose acetate of 39.43% acetyl content to a
4 cosolvent of methylene chloride and methanol to yield a solution effected by
5 stirring and warming. Next, the pore-former sorbitol is added to a cosolvent of
6 water and methanol with mixing followed by adding polyethylene glycol to
7 produce the outer coating solution. Finally, the outer coating solution is
8 coated around the subcoat in a pan coater and then dried for 18 hours at
9 45°C in a forced air oven, to yield the desired dosage form. The dosage form,
10 in operation in the gastrointestinal fluid of a human in need of drug therapy,
11 provides a uniform and nonvarying-order of drug release through exit
12 passageways of controlled porosity effected by the fluidic leaching of the
13 soluble pore-forming additive incorporated in the semipermeable outer coat.
14 The cooperation of the drug particles and the hydrophilic polymer particles
15 provides a viscous gel that pushes the drug through the exits at the
16 given rate.

17

18

EXAMPLE 4

19

20 The procedure of the above example is followed, with the proviso in
21 this example the therapeutic member is selected from the group consisting of
22 40 mg of simvastatin for lowering cholesterol, 75 mg of venlafaxine
23 antidepressant, 20 mg of fluoxetine antidepressant, 20 mg of antianginal
24 nifedipine, 40 mg of lovastatin indicated for lowering cholesterol, 20 mg of
25 enalapril maleate an angiotensin converting enzyme inhibitor, 120 mg of
26 diltiazem for managing calcium ion influx, 500 mg of ciprofloxacin
27 hydrochloride an antibacterial, 100 mg of sertraline hydrochloride an oral
28 antidepressant, 100 mg of cyclosporin an immunosuppressant, 1 mg of
29 terazosin hydrochloride an alpha-adrenoceptor blocker, 50 mg of sumatriptan
30 succinate a 5-hydroxytryptamine receptor agonist, 40 mg of pravastatin

1 sodium a hypolipidemic, 500 mg of an anti-HIV-proteinase inhibitor such as
2 nelfinavir, saquinavir, indinavir, or ritonavir, an anti-HIV such as zidovudine,
3 didanosine, or lamivudine, a reverse transcriptase inhibitor such as loviride,
4 an antiviral herpes such as fenciclovir or ganciclovir, 10 mg of alendronate
5 sodium for treating osteoporosis, and 2.5 mg of conjugated estrogen
6 indicated for the treatment of vasomotor symptoms associated with
7 menopause, atrophic vaginitis and osteoporosis loss of bone mass.

8 9 EXAMPLE 5

10
11 A dosage form for the oral uniform and nonvarying release of a drug
12 to a biological drug receptor is manufactured as follows: first, 6000g of
13 verapamil hydrochloride, indicated for the treatment of angina and high
14 blood pressure, having nonuniform particle size distribution between
15 1 micron to 900 micron, 3047g of poly(ethylene oxide) having a number
16 average molecular weight of 300,000 and having 25% particles greater
17 than 250 micron, 500g of sodium chloride and 100g of poly(vinylpyrrolidone)
18 having a number average molecular weight of 40,000 are added to a
19 Freund Flo-Coater's bowl, a fluid bed granulator. The bowl is attached to
20 the Flo-Coater and the granulation process is initiated. Next, the dry powders
21 are air suspended and mixed for five minutes. Then, a solution prepared by
22 dissolving 300g of poly(vinylpyrrolidone) having a number average molecular
23 weight of 40,000 in 4,500g of water is sprayed from 2 nozzles onto the
24 powder. The coating conditions are monitored during the
25 poly(vinylpyrrolidone) solution spraying as follows: a total spray rate of
26 240 g/min from each nozzle, an inlet temperature of 45°C, an airflow of
27 1000 cfm. The coating process is computerized and automated in cycles.
28 Each cycle contained 30 seconds of solution spraying followed by two
29 seconds of drying and 10 seconds of filter bags with shaking to unglue
30 any possible powder deposits. At the end of the solution spraying period,

1 the coated granulated particles are continued in the drying process for
2 25 minutes. The machine is turned off, and the coated granules are
3 removed from the coater. The coated granules are sized using a fluid air mill.
4 The granulation is transferred to a mixer, mixed and lubricated with 50g of
5 magnesium stearate and mixed with 4g of butylated hydroxytoluene, to
6 provide the drug composition.

7 Next, a push-displacement composition is prepared as follows:
8 first, 7342g of poly(ethylene oxide) possessing a number average
9 molecular weight of 7 million, 2000g of sodium chloride, 200g of
10 hydroxypropylmethylcellulose of 11,200 number average molecular weight,
11 100g of black ferric oxide are added to the Freund Flo-Coater's bowl.
12 The bowl is attached to the Flo-Coater and the granulation process is started
13 to effect the process. The dry powders are air suspended and mixed for
14 six minutes. Then, a solution is prepared by dissolving 300g of
15 hydroxypropylmethylcellulose having a number average molecular weight of
16 11,200 in 4,500g of water is sprayed from 2 nozzles onto the air suspended
17 powder mix. The coating conditions were monitored during the
18 hydroxypropylmethylcellulose spraying of the solution. The conditions are
19 identical to those described in the above drug granulation process, except
20 for the drying cycle of less than 25 minutes. The granulated powders are
21 removed from the granulator and sized in a fluid air mill. The granulation is
22 transferred to a blender, mixed and lubricated with 50g of magnesium
23 stearate and with 8 grams of butylated hydroxytoluene to yield the push-
24 displacement composition.

25 Next, the drug composition and the push composition are compressed
26 into a bilayered core. First, 300 mg of the drug composition comprising
27 180 mg of verapamil hydrochloride is added to the punch and tamped, then
28 100 mg of the push displacement composition is added to the punch and the
29 layers pressed under a pressure of 2200 pounds into a 13/32 inch (1.032 cm)
30 diameter contacting, bilayered arrangement.

1 Next, the bilayered core is coated with a subcoat. The subcoat
2 comprises 95% hydroxyethylcellulose of 90,000 number average molecular
3 weight and 5% polyethylene glycol of 3350 average molecular weight. The
4 ingredients are dissolved in water to make a 5% solid solution. The subcoat
5 forming composition is sprayed onto and around the bilayer core in a 24 inch
6 Vector Hi-Coater. The dry subcoat weighed 79 mg.

7 Next, the hydroxyalkylcellulose, a hydroxyethylcellulose, a subcoated
8 bilayered cores are over coated with a semipermeable composition. The
9 overcoat membrane forming composition comprises 60% cellulose acetate
10 having an acetyl content of 39.8%, 35% hydroxypropylcellulose of 40,000
11 number average molecular weight and 5% polyethylene glycol of 3350 avg.
12 molecular weight is dissolved in methylene chloride:methanol (90:10 wt:wt)
13 cosolvent to make a 4% solid solution. The semipermeable membrane
14 forming composition is sprayed onto and around the subcoated bilayer core.
15 The semipermeable membrane, after drying weighed 43 mg.

16 Next, two 27 mil (0.686 mm) exit passageways are drilled through the
17 outer semipermeable membrane and the inner subcoat to connect the drug
18 layer with the exterior of the dosage form. The residual solvents are removed
19 by drying for 96 hours at 50°C and 50% humidity. Finally, the dosage forms
20 are dried for 2 hours at 50°C to remove any excess moisture.

21 The dosage form manufactured by this procedure comprises a drug
22 composition with a weight of 300 mg, consisting of 180 mg of verapamil
23 hydrochloride, 91.41 mg of poly (ethylene oxide) of 300,000 molecular weight,
24 12 mg of poly(vinylpyrrolidone) of 40,000 molecular weight, 15 mg of sodium
25 chloride, 0.12 mg of butylated hydroxy toluene and 1.5 mg of magnesium
26 stearate. A push-displacement composition that weighs 100 mg consisting of
27 73.5 mg of poly(ethylene oxide) of 7,000,000 molecular weight 20 mg of
28 sodium chloride, 5 mg of hydroxypropylmethylcellulose of 11,200 molecular
29 weight, 0.92 mg of black ferric oxide, 0.08 mg of butylated hydroxytoluene and
30 0.5 mg of magnesium stearate. The dosage form subcoat weighed 78.8 mg

1 consisting of 74.86 mg of hydroxyethylcellulose of 90,000 molecular weight
2 and 3.94 mg of polyethylene glycol of 3350 molecular weight. The outer wall
3 weighed 42.6 mg consisting of 25.56 mg of cellulose acetate of 39.8% acetyl
4 content, 14.90 mg of hydroxypropylcellulose of 40,000 molecular weight, and
5 2.13 mg of polyethylene glycol of 3350 molecular weight. This dosage form
6 had a $(dm/dt)_i$ mean release rate of 18.6 mg/hr between the fourth and
7 ninth hour.

8 The delivery pattern for the dosage form prepared by this example is
9 illustrated in figure 1. In figure 1, the nonuniform variability release rate is
10 seen over the steady portion illustrated by the line starting at zero and
11 extended to the right of the figure. The release rate variation is for a drug
12 having a 1 to 900 micron particle size released in the presence of a
13 hydrophilic polymer having greater than 25% particles larger than 250 micron.
14 The solid line depicts the % deviation from the total mean release rate.
15 The mean release rate for a given dosage form is expressed by the number
16 along the line starting at zero. In the figure No. 1 the erratic behavior is
17 seen because the dosage form lacks uniform particles of a limited range.
18 The erratic behavior is characterized by a substantial deviation of individual
19 system from the mean (dosage form) steady state release rate performance.
20 This erratic behavior phenomena is attributed to the inability of the hydrophilic
21 polymer, the poly(ethylene oxide), to carry and suspend large drug
22 particles, (the verapamil hydrochloride), the difference in the hydration time
23 between the large and small drug particles, and the larger hydrophilic polymer
24 particles greater than 250 micron, which significantly changes the hydration
25 and the drug suspending properties of the drug compositional layer that
26 resulted into a large percent negative deviation in the $(dm/dt)_i$ from the
27 $(dm/dt)_0$. The expression $(dm/dt)_0$ denotes the total mean release rate for all
28 dosage forms in the zero portion, $(dm/dt)_i$ denotes the mean release rate of
29 an individual dosage form in 4 to 9 hours, and $(\% dev)_i$ denotes the percent

1 deviation in an individual dosage form mean release rate, (4 to 9 hours) from
2 the total mean release rate. The figure reports results obtained from the
3 following equation:

4

$$\begin{array}{l} 5 \quad (\% \text{ dev}) = \frac{(dm/dt)_i - (dm/dt)_t}{(dm/dt)_t} \\ 6 \end{array}$$

7

8

EXAMPLE 6

9

10 A dosage form for the delivery of a drug orally to a human is prepared
11 as follows: first 6000g of verapamil hydrochloride having a particle size of
12 less than 150 micron, 3047g of poly(ethylene oxide) possessing a number
13 average molecular weight of 300,000 with 25% particles larger than
14 250 micron, 500g of sodium chloride, 100g of poly(vinylpyrrolidone) having
15 a number average molecular weight of 40,000 are added to the bowl of a fluid
16 bed granulator. The granulation is carried out for 7 to 10 minutes. Next, the
17 dry powders are air suspended and mixed for five minutes. Then, a solution
18 is prepared by dissolving 300g of poly(vinylpyrrolidone) of 40,000 number
19 average weight in 4,500g of distilled water is sprayed from 2 nozzles onto the
20 dry powder. The coating conditions are monitored during spraying as follows:
21 a total spray rate of 240 g/min from each nozzle, an inlet temperature of 45°C
22 and a process airflow of 1000 cfm. The coated process is automated in
23 cycles. Each cycle consist of 30 seconds of solution spraying followed by
24 two seconds of drying and 10 seconds of filter bags shaking to unglue and
25 possible powder deposits. At the end of the solution spraying time, the
26 coated granulated particles are continued with the drying process for
27 25 minutes. The machine is turned off, and the coated granules were
28 removed from the coater. The coated granules are sized using a fluid air mill,
29 the granulation is transferred to a mixer, mixed and lubricated with 50 grams
30 of magnesium stearate and mixed with 4g of butylated hydroxytoluene to
31 provide the drug composition used for forming a layer in the bilayer core.

1 Next, a push composition is prepared as follows: first, 7342g of
2 poly(ethylene oxide) of 7,000,000 number average molecular weight, 2000g
3 of sodium chloride, 200g of hydroxypropylmethylcellulose of 11,200 number
4 average molecular weight, and 100 grams of black ferric oxide are added to
5 the bowl of a fluid bed granulator. The granulation process is started, and the
6 dry powders are air suspended and mixed for 6 minutes. Then, a solution is
7 prepared by dissolving 300g of hydroxypropylmethylcellulose possessing a
8 11,200 number average molecular weight in 4,500g of water that is sprayed
9 onto the air suspended powder mix. The coating conditions are monitored
10 during the spraying and the physical conditions are identical as described
11 for the above drug granulation, except that the drying cycle was less than
12 25 minutes. The granulated powders are removed from the granulator.
13 The granules are sized in a fluid air mill, then transferred to a blender and
14 lubricated while mixing with 50g of magnesium stearate and 8g of butylated
15 hydroxytoluene to yield the push composition.

16 Next, the drug composition and the push composition are pressed into
17 a bilayered core, with the layers in contacting arrangement. First, 400 mg of
18 the drug composition comprising 240 mg of verapamil hydrochloride is added
19 to a tablet punch and tamped, then 135 mg of the push composition is added
20 to the punch and the layers are pressed under a pressure head of 2300
21 pound in a 7/16 inch (1.11 cm) diameter contacting, bilayered arrangement.
22 The bilayered-core tablets are coated with a subcoat. The subcoat comprises
23 95% hydroxyalkylcellulose, a (hydroxyethylcellulose) of 90,000 molecular
24 weight and 5% polyethylene glycol of 3350 molecular weight, dissolved in
25 water to provide a 5% solid solution. The subcoat forming composition is
26 sprayed onto the around the bilayered core in a coater. The dry subcoat
27 weighed 93 mg.

1 Next, an outer coat is applied to the dosage form. The subcoated
2 bilayered-core tablets are coated with a semipermeable-membrane wall.
3 The membrane forming composition comprises 60% cellulose acetate having
4 a 39.8% acetyl content, 35% hydroxypropylcellulose of 40,000 molecular
5 weight and 5% polyethylene glycol of 3350 molecular weight. The wall
6 forming composition is dissolved in methylene chloride:methanol (90:10 wt:wt)
7 cosolvent to make a 4% solid solution. The semipermeable-membrane wall
8 forming composition is sprayed onto and around the subcoated bilayer core
9 in a coater to provide a two-coated dosage form. The semipermeable
10 membrane dry weighed 51 mg.

11 Next, two 27 mil (0.686 mm) exit passageways are drilled through the
12 outer and inner coats to connect the drug layer with the exterior of the dosage
13 form. The residual solvents are removed by drying for 96 hours at 50°C and
14 50% humidity. Then, the osmotic dosage forms are dried for 2 hours at 50°C
15 to remove excess moisture.

16 The dosage form manufactured by this procedure comprises a drug
17 composition with a weight of 400 mg, consisting of 240 mg of verapamil
18 hydrochloride, 121.88 mg of polyethylene oxide of 300,000 molecular weight,
19 16 mg of poly(vinylpyrrolidone) of 40,000 molecular weight, 20 mg of sodium
20 chloride, 2 mg of magnesium stearate and 0.16 mg of butylated
21 hydroxytoluene. The push composition of the dosage form weighed 135 mg
22 and consists of 99.23 mg of poly(alkylene oxide), poly(ethylene oxide) of
23 7,000,000 molecular weight, 27 mg of sodium chloride, 6.75 mg of
24 hydroxypropylmethylcellulose of 11,200 molecular weight, 1.24 mg of
25 ferric oxide, 0.675 mg magnesium stearate, and 0.108 mg of butylated
26 hydroxytoluene. The inner subcoat weighed 93.1 mg and consists of
27 88.45 mg of the hydroalkylcellulose, hydroxyethylcellulose of 90,000
28 molecular weight and 46.55 mg of polyethylene glycol of 3350 molecular
29 weight. The outer coat weighed 51.1 mg and consists of 30.66 mg of
30 cellulose acetate of 39.8% acetyl content, 17.89 mg of hydroxypropylcellulose

1 of 40,000 molecular weight and 2.57 mg of polyethylene glycol of 3350
2 molecular weight. The dosage form prepared by this example had a $(dm/dt)_t$
3 mean release rate of 27 mg/hr during hours 4 to 9.

4 The drug delivery pattern for the dosage form prepared by this
5 invention is seen in drawing figure 2. In figure 2, the nonuniform variability is
6 depicted for the dosage form. The erratic release behavior is characterized
7 by a substantial and pronounced deviation of individual dosage forms from
8 the mean dosage form steady state rate performance. The figure denotes
9 that larger polymer particles of from 250 micron significantly change the
10 hydration and the drug carrying ability and suspension properties of the
11 drug composition. This results in a large percent negative deviation in the
12 expression $(dm/dt)_t$ from the expression $(dm/dt)_t$.

13 14 EXAMPLE 7

15
16 A dosage form for the delivery of a drug orally to the gastrointestinal
17 tract of a human in need of drug therapy is prepared as follows: first, 6000g
18 of verapamil hydrochloride having a particle size of 150 or smaller microns,
19 3047g of poly(ethylene oxide) of 300,000 molecular weight and having a
20 particle of 250 or smaller microns, 500g of powdered sodium chloride, 100g of
21 poly(vinylpyrrolidone) having a 40,000 molecular weight are added to a coater
22 and granulated in air for five minutes. Next, a solution is prepared by
23 dissolving 300g of poly(vinylpyrrolidone) of 40,000 molecular weight in 4,500g
24 of water and sprayed onto the powder. The spray rate is 240g/min at an inlet
25 temperature of 45°C and an airflow of 1000 cfm. The spraying is effected in
26 two cycles consisting of 30 seconds of solution spraying followed by two
27 seconds of drying and 10 seconds of shaking to unglue powder deposits.
28 At the end of the solution spraying period, the coated granulated particles are
29 dried for an additional 25 minutes. Then, the coated granules are sized in a
30 fluid air mill. The granulation is transferred to a mixer, and lubricated with

1 50g of magnesium stearate and with 4g of butylated hydroxytoluene, to
2 yield the drug composition.

3 Next, a push displacement composition is prepared as follows:
4 first, 7342g of poly(ethylene oxide) of 7,000,000 molecular weight, 2000g
5 of sodium chloride, and 2000g of hydroxypropylmethylcellulose of 11,200
6 molecular weight, and 100g (grams) of black ferric oxide are added to the
7 bowl of a fluid bed granulator. The granulation is started and the powders
8 mixed for six minutes. Then, a solution is prepared by dissolving 300g of
9 hydroxypropylmethylcellulose of 11,200 molecular weight in water and
10 sprayed onto the air suspended particles. The coating process is as
11 described above. The granules are sized in a fluid air mill and transferred to
12 a blender, and blended with 50g of magnesium stearate and 8g of butylated
13 hydroxytoluene, to yield the push-displacement composition.

14 Next, the drug composition and the push composition are compressed
15 into a bilayered tablet as follows: first, 400 mg of the drug composition
16 containing 240 mg of verapamil hydrochloride is added and tamped, then it
17 is overlayed with 135 mg of the push composition, and the two compositions
18 pressed under 2300 pounds into a 7/16 inch (1.11 cm) diameter contacting,
19 bilayered arrangement.

20 Next, the compressed bilayer tablets are coated with a subcoat
21 laminate. The subcoat comprises 95% hydroxyethylcellulose of 90,000
22 molecular weight and 5% polyethylene glycol of 3350 molecular weight
23 dissolved in distilled water to make a solid solution. The subcoat forming
24 composition is sprayed onto and around the bilayered tablet in a coater
25 to provide an encompassing laminate. The dry subcoat weighed 93 mg.

26 Next, the subcoat is overcoated with a semipermeable wall.
27 The semipermeable composition comprises 60% cellulose acetate having
28 an acetyl content of 39.8%, 35% hydroxypropylcellulose of 40,000 molecular
29 weight and 5% polyethylene glycol of 3350 average molecular weight.

1 The wall-forming composition is dissolved in a methylene-chloride:methanol
2 (90:10 wt:wt) cosolvent to make a 4% solid solution. The semipermeable
3 overcoat is sprayed onto and around to encase the subcoat. The
4 semipermeable wall weighed 51 mg.

5 Next, two 27 mil (0.686 mm) exit passageway are drilled through the
6 dual coats to connect the drug layer with the exterior of the dosage form.
7 The residual solvents are removed by drying for 96 hours at 50°C and
8 50% humidity. Next, the osmotic, fluid imbibing dosage forms are dried
9 for 2 hours at 50°C to remove excess moisture.

10 The dosage form prepared by this example embraces the same
11 composition as the example immediately above, except for the controlled
12 drug particle size and the controlled hydrophilic polymer particle size in the
13 drug composition. This double particle control produces substantially uniform
14 dose dispensing, substantially-free of a wide variation in the dose dispensing
15 pattern. Accompanying figure 3 depicts the drug delivery pattern for this
16 example. The figure depicts a release rate of (dm/dt) , equal to 27.9 mg/hr
17 during hours 4 to 9. The figure illustrates that a nonuniform variability is not
18 observed for the dosage form provided by this example.

19

20

EXAMPLE 8

21

22 A dosage form prepared according to Example 8 wherein the drug in
23 the dosage form is a calcium channel blocking drug selected from the group
24 consisting of isradipine, nilvadipine, flunarizine, nimodipine, diltiazem,
25 nicardipine, nitredipine, nisoldipine, flodipine, amlodipine, cinnarizine,
26 and fendiline.

EXAMPLE 9

The procedure described in the above is repeated in this example, with the processing conditions as previously set forth, except that, in this example the drug is an angiotensin converting enzyme inhibitor selected from the group consisting of alacipril, benazepril, cialzepril, captopril, delapril, enalapril, fosinopril, lisinopril, moveltypril, perindopril, quinapril, ramipril, spirapril, and zofenopril.

EXAMPLE 10

The procedures of the above examples are followed in this example with the addition of the drug and is protected against oxidative attack and oxidation by adding to the processing drug composition 0.05 ng to 7 mg of an antioxidant selected from the group consisting of d-alpha tocopherol, dl-alpha tocopherol, d-alpha tocopherol acetate, d-alpha tocopherol acid succinate, dl-alpha tocopherol acid succinate, dl-alpha tocopherol palmitate, ascorbic acid, ascorbyl oleate, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, sodium ascorbate, calcium ascorbate, and propyl gallate stabilizers.

EXAMPLE 11

The procedures of the above examples are followed in this example with an addition to the drug composition comprising 0.05 ng to 7 mg of an antioxidant stabilizer and 0.05 ng to 7.5 mg of a lubricant selected from the group consisting of magnesium stearate, calcium stearate, magnesium oleate, magnesium palmitate, corn starch, potato starch, bentonite, citrus pulp, and stearic acid; and, with all the ingredients in the drug composition when expressed in weight percent equal to 100 wt% weight percent.

EXAMPLE 12

The procedures of the above examples are followed in this example with an addition to the drug composition of means protection the drug against daylight and ultraviolet light; wherein, the addition comprising adding to the drug composition 0.01 mg to 10 mg of surface-active agent selected from anionic, cationic, amphoteric and nonionic surfactants including dialkyl sodium sulfosuccinate, polyoxyethylene glycerol, polyoxyethylene stearyl ether, propoxy-ethoxy copolymer, polyoxyethylene fatty alcohol ester, polyoxyethylene fatty acid ester, ethoxylated hydrogenated castor oil, and butoxylated hydrogenated castor oil; and adding to the drug composition 0.01 mg to 10 mg of riboflavin to stabilize the drug against light.

ADDITIONAL DISCLOSURE OF THE INVENTION

In the specification and in the accompanying claims, the term beneficial agent also includes drugs. The term drug includes any physiologically or pharmacologically active substance that produces a local or a systemic effect, in animals, including warm-blooded mammals, humans and primates; avians, household, sport, and farm animals; laboratory animals; fishes; reptiles; and zoo animals. The term "physiologically" as used herein, generically denotes the administration of a drug to produce generally normal drug levels and functions. The term "pharmacologically" denotes generally variations in response to the amount of drug administered to a host. The drug can be in various forms such as unchanged molecules, molecular complexes, pharmacologically acceptable salts such as hydrochloride, hydrobromide, sulfate, laurate, palmitate, phosphate, nitrite, nitrate, borate, acetate, maleate, tartiate, oleate, salicylate, and the like. For acidic drugs, salts of metals, amines, or organic cations, for example quarternary ammonium can be used. Derivatives of drugs, such as bases, ester and amide can be used. A drug

1 that is water insoluble can be used in a form that is water soluble derivative
2 thereof, or as a base derivative thereof, which in either instance or in its
3 delivery by the osmotic system, is converted by enzymes, hydrolyzed by the
4 body pH, or by other metabolic processes to the original therapeutically active
5 form. The amount of drug in a dosage form, that is, in the drug composition is
6 25 ng to 750 mg. The dosage form comprising the drug can be administered,
7 once, twice, or thrice daily.

8 The active drug that can be delivered includes inorganic and organic
9 compounds without limitation, including drugs that act on the peripheral
10 nerves, adrenergic receptors, cholinergic receptors, nervous system, skeletal
11 muscles, cardiovascular system, smooth muscles, blood circulatory system,
12 synaptic sites, neuroeffector junctional sites, endocrine system, hormone
13 systems, immunological system, organ systems, reproductive system,
14 skeletal system, autocrine systems, alimentary and excretory systems,
15 inhibitory of autocrine and histamine systems, and physiological systems.
16 The active drug that can be delivered for acting on these animal systems
17 includes depressants, beta-blockers, hypnotics, sedatives, psychic
18 energizers, tranquilizers, anti-convulsants, muscle relaxants, steroids,
19 antiparkinson agents, analgesics, anti-inflammatories, polypeptides, local
20 anesthetics, muscle contractants, anti-microbials, antimalarials, hormonal
21 agents, contraceptives, sympathomimetics, diuretics, anti-parasitics,
22 neoplastics, hypoglycemics, ophthalmics, electrolytes, diagnostic agents,
23 cardiovascular drugs, calcium channel blockers, angio-tensin-converting
24 enzyme inhibitors, and the like.

25 Exemplary of drugs that can be delivered from the dosage form of
26 this invention include a drug selected from the group consisting of amifostine,
27 prochlorperazine edisylate, ferrous sulfate, aminocaproic acid, potassium
28 chloride, mecamylamine hydrochloride, procainamide hydrochloride,
29 amphetamine sulfate, benzphetamine hydrochloride, isoproterenol sulfate,
30 methamphetamine hydrochloride, phenmetrazine hydrochloride, bethanechol

1 chloride, methacholine chloride, pilocarpine hydrochloride, antropine sulfate,
2 methascopolamine bromide, isopropamide iodide, tridihexethyl chloride,
3 phenformin hydrochloride, methylphenidate hydrochloride, oxprenolol
4 hydrochloride, metoprolol tartrate, cimetidine hydrochloride, diphenidol,
5 meclizine hydrochloride, prochlorperazine maleate, phenoxybenzamine,
6 thiethylperzine, maleate, anisindone, diphenadione erythrityl terantrate,
7 dizozin, isofurophate, reserpine, acetazolamide, methazolamide,
8 bendroflumenthiazide, chlorpropamide, tolazamide, chlormadinone acetate,
9 phenaglycodol, allopurinol, aluminum aspirin, methotrexate, acetyl
10 sulfisoxazole, erythromycin, progestins, estrogenic progestational,
11 corticosteroids, hydrocortisone acetate, cortisone acetate, triamcinolone,
12 methyltestosterone, 17 β -estradiol, ethinyl estradiol, ethinyl estradiol 3-methyl
13 ether, prednisolone, 17-hydroxyprogesterone acetate, 19-nor-progesterone,
14 norgestrel, norethindone, norethiderone, progesterone, norgestron,
15 orethynodrei, aspirin, indomethacin, aproxen, fenoprofen, sulidac, diclofenac,
16 indoprofen, nitroglycerin, propranolol, metoprolol, vallproate, oxyprenolol,
17 timolol, atenolol, alpreholol, cimetidine, clonidine, imipramine, levodopa,
18 chloropropmazine, reserpine, methylidopa, dihydroxyphenyllalanine,
19 pivaloyloxyethyl ester of ϵ -methylidopa hydrochloride, theophylline, calcium
20 gluconate ferrous lactate, ketoprofen, ibuprofen, cephalixin, erythromycin,
21 haloperidol, zomepirac, vincamine, diazepam, phenoxybenzamine,
22 β -blocking agents; calcium-channel blocking drugs such as nifedipine,
23 diltiazem, isradipine, nilvadipine verapamil, flunarizine, nimodipine, felodipine,
24 amlodipine, cinnarizine and fendiline; angiotensin converting enzyme
25 inhibitors selected from the group consisting of angiotensin converting
26 enzyme inhibitors that are essentially free of sulfur, angiotensin converting
27 enzyme inhibitors containing a sulfhydryl group, angiotensin converting
28 enzyme inhibitors containing a linear sulfide, angiotensin converting enzyme
29 inhibitors containing a cyclic sulfide angiotensin converting enzyme inhibitors
30 containing a methylsulfonyl group and angiotensin enzyme inhibitors

1 represented by a member selected from the group consisting of ramipril,
2 fosinopril, altiopril, benazepril, libenzapril, alacepril, citazapril, cilazaprilate,
3 perindopril, zofenopril, enalapril, lisinopril, imidapril, spirapril, rentrapril,
4 captopril, delapril, alindapril, indolapril, and quinapril; propranolol, naproxen,
5 phenylpropanolamine, glipizide, venlafaxine, and beneficial drugs known to
6 the dispensing arts in Pharmaceutical Sciences, 1990, edited by Remington
7 18th Edition published by Mack Publishing Co., Easton, PA; Physicians' Desk
8 Reference, 50th Edition, (1996) published by Medical Economics Co.,
9 Montvale, NJ, and, USP Dictionary, 1995, published by the United States
10 Pharmacopeial Convention, Inc., Rockville, Maryland.

11 The dosage form of the invention is provided with at least one exit
12 means. The exit means cooperates with the drug core for the uniform and
13 substantially nonvarying drug-dose release from the dosage form. The exit
14 means can be provided during manufacture of the dosage form, or the exit
15 means can be provided during drug delivery by the dosage form in fluid
16 environment of use. The expression exit means, as used for the purpose of
17 this invention, included a member selected from the group consisting of
18 passageway, aperture, orifice, bore, pore, micropore, porous element
19 through which a drug can be pumped, diffuse, travel, or migrate, a hollow
20 fiber, capillary tube, porous insert, porous overlay, microporous member,
21 and porous composition. The expression includes also a compound or
22 polymer that erodes, dissolves or is leached from the outer coat or wall,
23 or from the inner coat to form at least one exit, or a multiplicity of exits.
24 The compound or polymer includes an erodible poly (glycolic) acid or
25 poly (lactic) acid in the outer or inner coats, a gelatinous filament,
26 a water-removable poly (vinyl alcohol), a leachable compound such as
27 a fluid removable pore-former selected from the group consisting of an
28 inorganic, organic, acid, salt, oxide, and carbohydrate. An exit or a plurality
29 of exits can be formed by leaching a member selected from the group
30 consisting of sorbitol, lactose, fructose, glucose, mannose, galactose, talose,

1 sodium chloride, potassium chloride, sodium citrate, and mannitol; to provide
2 an uniform-release dimensioned pore-exit means. The exit means can have
3 any shape such as round, triangular, square, elliptical and the like for the
4 uniform-metered dose release of a drug from the dosage form. The dosage
5 form can be constructed with one or more than one exits in spaced apart
6 relation or one or more than one surface of the dosage form. The exit means
7 can be performed by drilling including mechanical and laser drilling through
8 the outer, or inner or through both coats. Exits and equipment for forming
9 exits are disclosed in U.S. Pat. Nos. 3,845,770 and 3,916,899 by Theeuwes
10 and Higuchi; in U.S. Pat. Nos. 4,063,064 by Saunders, et al; and in U.S. Pat.
11 No. 4,088,864 by Theeuwes, et al. Exit means comprising dimension, sized,
12 shaped and adapted as a releasing-pore formed by aqueous leaching to
13 provide a drug releasing pore are disclosed in U.S. Pat. Nos. 4,200,098
14 and 4,285,987 by Ayer and Theeuwes.

15 The particles used for the purpose of this invention are produced by
16 comminution that produces the size of the drug and the size of the
17 accompanying hydrophilic polymer used according to the mode and the
18 manner of the invention. The means for producing particles include spray
19 drying, sieving, lyophilization, sieving, crushing, grinding, jet milling
20 micronizing and chopping to produce the intended micron particle size.
21 The process can be performed by size reduction equipment such as
22 micropulverizer mill, fluid energy grinding mill, grinding mill, roller mill,
23 hammer mill, attrition mill, chaser mill, ball mill, vibrating ball mill, impact
24 pulverizer mill, centrifugal pulverizer, coarse crusher and fine crusher.
25 The size of the particle can be ascertained by screening including grizzly
26 screen, flat screen, vibrating screen, revolving screen, shaking screen,
27 oscillating screen and reciprocating screen. The processes and the
28 equipment for preparing particles are disclosed in Pharmaceutical Sciences
29 by Remington, 17th Ed., pg. 1585-1594, (1985); Chemical Engineers:
30 Handbook, by Perry, Sixth Edition, pg. 21-13 to 21-19 (1984); Journal of

1 Pharmaceutical Sciences, by Parrot, Vol. 61, No., 6, pg. 813 to 829 (1974);
2 and Chemical Engineer, by Hixon, pg. 94 to 103, (1990).

3 In accordance with the practice of this invention, it has now been found
4 the dosage can be provided with a semipermeable wall, also identified for
5 the purpose of this invention as an outercoat. The semipermeable wall is
6 permeable to the passage of an external fluid such as water and biological
7 fluids, and it is substantially impermeable to the passage of a beneficial agent,
8 as osmogen, an osmopolymer, and the like. The selectively semipermeable
9 compositions used for forming the wall are essentially non-erodible and they
10 are insoluble in biological fluids during the life of the dosage form.

11 Representative polymers for forming the wall comprise semipermeable
12 homopolymers, semipermeable copolymers, and the like. In one presently
13 preferred embodiment, the compositions comprise cellulose esters, cellulose
14 ethers, and cellulose ester-ethers. The cellulosic polymers have a degree
15 of substitution, D.S. of their anhydroglucose unit from greater than 0 up
16 to 3 inclusive. By degree of substitution is meant the average number
17 of hydroxyl groups originally present on the anhydroglucose unit that
18 are replaced by a substituting group, or converted into another group.
19 The anhydroglucose unit can be partially or completely substituted with
20 groups such as acyl, alkanoyl, alkenoyl, aroyl, alkyl, alkoxy, halogen,
21 carboalkyl, alkylcarbamate, alkylcarbonate, alkylsulfonate, alkylsulfamate,
22 semipermeable polymer forming groups, and the like.

23 The semipermeable compositions typically include a member selected
24 from the group consisting of cellulose acylate, cellulose diacylate, cellulose
25 triacylate, cellulose triacetate, cellulose acetate, cellulose diacetate, cellulose
26 triacetate, mono-, di- and tri-cellulose alkanylates, mono-, di-, and tri-
27 alkenylates, mono-, di-, and tri-aroylates, and the like. Exemplary polymers
28 include cellulose acetate having a D.S. of 1.8 to 2.3 and an acetyl content of
29 32 to 39.9%; cellulose diacetate having a D.S. of 1 to 2 and an acetyl content
30 of 21 to 35%, cellulose triacetate having a D.S. of 2 to 3 and an acetyl content

1 of 34 to 44.8%, and the like. More specific cellulosic polymers include
2 cellulose propionate having a D.S. of 1.8 and a propionyl content of 38.5%;
3 cellulose acetate propionate having an acetyl content of 1.5 to 7% and an
4 acetyl content of 39 to 42%; cellulose acetate propionate having an acetyl
5 content of 2.5 to 3%, an average propionyl content of 39.2 to 45%, and a
6 hydroxyl content of 2.8 to 5.4%; cellulose acetate butyrate having a D.S.
7 of 1.8, an acetyl content of 13 to 15%, and a butyryl content of 34 to 39%;
8 cellulose acetate butyrate having an acetyl content of 2 to 29%, a butyryl
9 content of 17 to 53%, and a hydroxyl content of 0.5 to 4.7%; cellulose
10 triacylates having a D.S. of 2.6 to 3 such as cellulose trivalerate, cellulose
11 trilaminate, cellulose tripalmitate, cellulose trioctanoate, and cellulose
12 tripropionate; cellulose diesters having a D.S. of 2.2 to 2.6 such as cellulose
13 disuccinate, cellulose dipalmitate, cellulose dioctanoate, cellulose dicarpylate,
14 and the like; mixed cellulose esters such as cellulose acetate valerate,
15 cellulose acetate succinate, cellulose propionate succinate, cellulose acetate
16 octanoate, cellulose valerate palmitate, cellulose acetate heptonate, and the
17 like. Semipermeable polymers are known in US Pat. No. 4,077,407 and they
18 can be synthesized by procedures described in Encyclopedia of Polymer
19 Science and Technology, Vol. 3, pages 325 to 354, 1964, published by
20 Interscience Publishers, Inc., New York.

21 Additional semipermeable polymers for forming the outer wall comprise
22 cellulose acetaldehyde dimethyl acetate; cellulose acetate ethylcarbamate;
23 cellulose acetate methyl carbamate; cellulose dimethylaminoacetate;
24 semipermeable polyamide; semipermeable polyurethanes; semipermeable
25 sulfonated polystyrenes; cross-linked selectively semipermeable polymers
26 formed by the coprecipitation of a polyanion and a polycation as disclosed
27 in U.S. Pat. Nos. 3,173,876; 3,276,586; 3,541,005; 3,541,006; and 3,546,142;
28 semipermeable polymers as disclosed by Loeb et al in U.S. Pat.
29 No. 3,133,132; semipermeable polystyrene derivatives; semipermeable

1 poly (sodium styrenesulfonate); semipermeable poly
2 (vinylbenzyltrimethylammonium chloride); semipermeable polymers,
3 exhibiting a fluid permeability of 10^{-5} to 10^{-2} (cc. mil/cm hr.atm) expressed
4 as per atmosphere of hydrostatic or osmotic pressure differences across a
5 semipermeable wall. The polymers are known to the art in U.S. Pat.
6 Nos. 3,845,770; 3,916,899; and 4,160,020; and in Handbook of Common
7 Polymers, by Scott, J.R., and Roff, W.J., 1971, published by CRC Press,
8 Cleveland, Ohio.

9 The subcoat of the invention is in contacting position with the
10 inner surface of the semipermeable wall, which outer semipermeable
11 wall surrounds and encases the inner subcoat. The inner subcoat is
12 0.01 mm to 3 mm thick and it comprises a member selected from
13 group consisting of hydroxyalkyl, hydroxyethylcellulose,
14 hydroxyisopropylcellulose, hydroxybutylcellulose, and hydroxyphenylcellulose.
15 The hydroxyalkylcellulose comprises a 9,500 to 1,250,000 number average
16 molecular weight.

17 The drug composition comprised a hydrophilic polymer for providing
18 in the drug composition a hydrophilic polymer particle that contributes to the
19 uniform and nonvarying drug delivery pattern. Representatives of these
20 polymers comprise a member selected from the group consisting of a poly
21 (alkylene oxide) of 100,000 to 750,000 number average molecular weight
22 including poly (ethylene oxide), poly (methylene oxide), poly (butylene oxide),
23 and poly (hexylene oxide); and a poly (carboxymethylcellulose) of 40,000 to
24 400,000 number average molecular weight represented by poly (alkali
25 carboxymethylcellulose), poly (sodium carboxymethylcellulose), poly
26 (potassium carboxymethylcellulose), and poly (lithium
27 carboxymethylcellulose). The drug composition can comprise a
28 hydroxypropylalkylcellulose of 9,200 to 125,000 number average
29 molecular weight for enhancing the delivery properties of the dosage

1 form as represented by hydroxypropylethylcellulose,
2 hydroxypropylmethylcellulose, hydroxypropylbutylcellulose, and
3 hydroxypropylpentylcellulose; and a poly (vinylpyrrolidone) of
4 7,000 to 75,000 number average molecular weight for enhancing
5 the flow properties of the dosage form.

6 The push-displacement composition in contacting layered arrangement
7 comprised a polymer that imbibes an aqueous or biological fluid and swells to
8 push the drug composition through the exit means from the dosage form.
9 Representative of fluid-imbibing displacement polymers comprise a member
10 selected from the group consisting of a poly (alkylene oxide) of 1,000,000 to
11 15,000,000 number average molecular weight as represented by poly
12 (ethylene oxide) and a poly (alkali carboxymethylcellulose) of 500,000 to
13 3,500,000 number average molecular weight wherein the alkali is sodium,
14 potassium or lithium. Examples of further polymers for formulation, the push-
15 displacement composition comprise osmopolymers comprise polymers that
16 form hydrogels such as Carbopol® acidic carboxypolymer, a polymer of
17 acrylic and cross-linked with a polyallyl sucrose, also known as
18 carboxypolymethylene and carboxyvinyl polymer having a molecular weight
19 of 250,000 to 4,000,000; Cyanamer® polyacrylamides; cross-linked water
20 swellable indenemaleic anhydride polymers; Good-rite® polyacrylic acid
21 having a molecular weight of 80,000 to 200,000; Aqua-Keeps® acrylate
22 polymer polysaccharides composed of condensed glucose units such as
23 diester cross-linked polygluran; and the like. Representative polymers that
24 form hydrogels are known to the prior art in U.S. Pat. No. 3,865,108 issued
25 to Hartop; U.S. Pat No. 4,002,173 issued to Manning; U.S. Pat. No.
26 4,207,893 issued to Michaels; and in Handbook of Common Polymers,
27 by Scott and Roff, published by the Chemical Rubber Co., Cleveland, Ohio.

28 The osmagent, also known as osmotic solute and as osmotically
29 effective agent, that exhibits an osmotic pressure gradient across the outer
30 wall and subcoat comprises a member selected from the group consisting of

1 sodium chloride, potassium chloride, lithium chloride, magnesium sulfate,
2 magnesium chloride, potassium sulfate, sodium sulfate, lithium sulfate,
3 potassium acid phosphate, mannitol, urea, inositol, magnesium succinate,
4 tartaric acid raffinose, sucrose glucose, lactose, sorbitol, inorganic salts,
5 organic salts and carbohydrates.

6 Exemplary solvents suitable for manufacturing the hydroactivated layer
7 and the wall comprise inert inorganic solvents that do not adversely harm the
8 materials, the capsule, and the final laminated wall hydro-activated layer.
9 The solvents broadly include members selected from the group consisting of
10 aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons,
11 halogenated solvents, cycloaliphatic, aromatics, heterocyclic solvents and
12 mixtures thereof. Typical solvents include acetone, diacetone alcohol,
13 methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl
14 acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl
15 propyl ketone, n-hexane, n-heptane, ethylene glycol monoethyl ether,
16 ethylene glycol monomethyl acetate, methylene dichloride, ethylene dichloride,
17 propylene dichloride, carbon tetrachloride nitroethane, nitropropane
18 tetrachloroethane, ethyl ether, isopropyl ether, cyclohexane, cyclooctane,
19 benzene, toluene, naphtha, 1,4-dioxane, tetrahydrofuran, diglyme, water,
20 aqueous solvents containing inorganic salts such as sodium chloride,
21 calcium chloride, and the like, and mixture thereof such as acetone and
22 water, acetone and methanol, acetone and ethyl alcohol, methylene
23 dichloride and methanol, and ethylene dichloride and methanol.

24 The semipermeable wall and the subcoat of the dosage form can
25 be formed in one technique using the air suspension procedure. This
26 procedure consists of suspending and tumbling the bilayer core in a current
27 of air, an inner subcoat composition and an outer semipermeable wall forming
28 composition, until in either operation the subcoat and the outer wall coat is
29 applied to the bilayer core. The air suspension procedure is well-suited for
30 independently forming the wall of the dosage form. The air suspension

1 procedure is described in U.S. Pat. No. 2,799,241; in J. Am. Pharm. Assoc.,
2 Vol. 48, pp. 451 to 459, (1959); and, *ibid*, Vol. 49, pp. 82 to 84, (1960).

3 The dosage form also can be coated with a Wurster® air suspension coater,
4 using for example, methylene dichloride methanol as a cosolvent.

5 An Aeromatic® air suspension coater can be used employing a cosolvent.

6 Other coating techniques, such as pan coating, can be used for providing
7 the dosage form. In the pan coating system, the subcoat on the wall forming
8 compositions are deposited by successive spraying of the respective
9 compensation on the bilayered core accompanied by tumbling in a rotating
10 pan. A pan coater is used because of its availability at commercial scale.

11 Other techniques can be used for coating the drug core. Finally, the wall or
12 coated dosage form are dried in a forced air oven at 40°C. for a week, or in
13 a temperature and humidity controlled oven for 24 hours at 40°C. and 50%
14 relative humidity to free the dosage form of solvent.

15 The dosage form of the invention is manufactured by standard
16 techniques. For example, in one manufacture, the beneficial drug and other
17 ingredients comprising the first layer facing the exit means are blended and
18 pressed into a solid layer. The layer possesses dimensions that correspond
19 to the internal dimensions of the area the layer is to occupy the dosage
20 form and it also possesses dimensions corresponding to the second layer for
21 forming a contacting arrangement therewith. The drug and other ingredients
22 can be blended also with a solvent and mixed into a solid or semisolid form by
23 conventional methods, such as ballmilling, calendering, stirring or rollmilling,
24 and then pressed into a preselected shape. Next, a layer of osmopolymer
25 composition is placed in contact with the layer of drug in a like manner.
26 The layering of the drug formulation and the osmopolymer layer can be
27 fabricated by conventional two-layer press techniques. The two contacted
28 layers are first coated with a subcoat and an outer semipermeable wall.
29 The air suspensions and air tumbling procedures comprises in suspending

1 and tumbling the pressed, contacting first and second layers in a current of
2 air containing the delayed-forming composition until the first and second
3 layers are surrounded by the wall composition.

4 In another manufacture, the dosage form is manufactured by the wet
5 granulation technique. In the wet granulation technique, the drug and the
6 ingredients comprising the first layer or drug composition, are blended using
7 an organic solvent, such as denature anhydrous ethanol, as the granulation
8 fluid. The ingredients forming the first layer or drug composition are
9 individually passed through a preselected screen and then thoroughly
10 blended in a mixer. Next, other ingredients comprising the first layer can
11 be dissolved in a portion of the granulation fluid, the solvent described above.
12 Then, the latter prepared wet blend is slowly added to the drug blend with
13 continual mixing in the blender. The granulating fluid is added until a wet
14 blend is produced, which wet mass blend is then forced through a
15 predetermined screen onto oven trays. The blend is dried for 18 to 24 hours
16 at 24°C. to 35°C. in a forced air oven. The dried granules are then sized.
17 Next, magnesium stearate is added to the drug granulation, it is then put
18 into milling jars and mixed on a jar mill for 10 minutes. The composition is
19 pressed into a layer, for example, in a Manesty® press. The speed of the
20 press is set at 20 rpm and the maximum load set at 2 tons. The first layer
21 is pressed against the composition forming the second layer and the bilayer
22 tablets are fed to the Kilian® dry Coata press and surrounded with the drug-
23 free coat, followed by the exterior wall solvent coating.

24 Another manufacturing process that can be used for providing
25 the compartment-forming composition comprises blending the powdered
26 ingredients in a fluid bed granulator. After the powdered ingredients
27 are dry blended in the granulator, a granulating fluid, for example,
28 poly(vinylpyrrolidone) in water, is sprayed onto the powders. The coated
29 powders are then dried in the granulator. This process granulates all the
30 ingredients present therein while adding the granulating fluid. After the

1 granules are dried, a lubricant such as stearic acid or magnesium stearate is
2 mixed into the granulation, using a V-blender. The granules are then pressed
3 in the manner described above.
4

5 METHOD OF PRACTICING THE INVENTION 6

7 The invention provides a process for the substantially uniform and
8 substantially nonvarying rate of release of a drug from a dosage form, herein
9 the dosage form comprises a composition, a dose of drug in the composition,
10 and a hydrophilic polymer in the composition, and wherein the process
11 comprises (1) formulating the composition with a drug possessing, a particle
12 size up to and including 150 microns, and (2) formulating the composition
13 with a hydrophilic polymer possessing a particle size up to and including
14 250 microns, hereby, through the copresence of (1) and (2) in the
15 composition, the drug is delivered as the substantially uniform and
16 nonvarying rate of release from the dosage form.

17 The invention provides also a process for substantially uniform
18 and substantially nonvarying rate of release of a drug from a dosage form,
19 wherein the dosage form comprises a composition, a dose of drug in the
20 composition, a hydrophilic polymer in the composition, and a composition
21 for displacing the drug composition from the dosage form, and wherein the
22 process comprises (1) formulating the composition with a drug possessing
23 a particle size up to and including 150 micron, (2) formulating the
24 composition with a hydrophilic polymer possessing a particle size up to
25 and including 150 microns, whereby through the copresence of (1) and
26 (2) in combination with the composition for displacing the drug composition
27 imbibing fluid, expanding and displacing the drug composition from the
28 dosage form. The drug is delivered at a substantially uniform and nonvarying
29 rate of release over time.

1 The invention comprises also a method for delivering a drug to a
2 patient, wherein the method comprises: (A) admitting orally into the patient a
3 dosage form comprising: (1) a semipermeable wall that surrounds and forms
4 a compartment; (2) a drug composition in the compartment; (3) a dose of
5 drug particles up to 150 micron in the drug composition; (4) a hydrophilic
6 polymer of up to 250 micron in the drug composition; (5) an exit in the
7 semipermeable wall; (B) imbibing fluid through the semipermeable wall
8 into the drug composition whereby through the coaction of (2) and
9 (3) a dispensable drug composition is formed in the dosage form; and
10 (C) delivering the drug composition through the exit to a patient at a
11 substantially uniform and nonvarying dose over time.

12 The invention comprises further a method for providing a drug-free
13 interval by placing a subcoat in the dosage form in contact with the inside
14 surface of the semipermeable wall and surrounding the drug composition,
15 or surrounding both a drug composition and a push composition, which
16 drug-free interval is followed in 2 to 5 hours by a drug delivery period of
17 1 to 15 hours. The latter method is indicated for the treatment of
18 hypertension and angina as it provides a drug-free interval when a patient
19 is less active, thus, at rest or when asleep, and the inventive method then
20 provides drug during the rising and waking hours mainly during the time
21 when activity reaches a maximum during the daytime hours.

22 The method of the invention pertains also to the management of
23 blood pressure, the management of the systemic physiology, and to the
24 management of chronotherapy, that is timetherapy by administering a
25 drug according to the mode and the manner of the invention.

26 The novel dosage form of this invention uses dual means for the
27 attainment of precise release rate of drugs that are difficult to deliver in the
28 environment of use, while simultaneously maintaining the integrity and the
29 character of the system. While there has been described and pointed out

1 features and advantages of the invention, as applied to the presently
2 preferred embodiments, those skilled in the dispensing art will appreciate
3 that various modifications, changes, additions, and omissions in the system
4 illustrated and described can be made without departing from the spirit of
5 the invention.

1 The Claims:

2

3 1. A process for providing a substantially uniform drug rate of
4 release from a dosage form, wherein the dosage form comprises a
5 composition, a dose of drug in the composition, and a hydrophilic polymer
6 in the composition; and wherein the process comprises (1) formulating the
7 composition with a drug possessing a size less than 150 micron, and
8 (2) formulating the composition with a hydrophilic polymer of less than
9 250 micron; whereby, through the copresence of (1) and (2) in the
10 composition, the drug is delivered at a substantially uniform rate of release
11 from the dosage form.

12 2. The process for providing the substantially uniform drug rate of
13 release from the dosage form according to Claim 1, wherein the composition
14 is enveloped by a wall comprising means for releasing the drug from the
15 dosage form.

16 3. The process for providing the substantially uniform drug rate of
17 release from the dosage form according to Claim 1, wherein the composition
18 is surrounded by an outer wall and an inner subcoat, with means in the
19 dosage form for releasing the drug from the dosage form.

20 4. A process for providing a substantially uniform drug rate of
21 release from a dosage form, wherein the dosage form comprises: a drug
22 layer comprising a dose of drug and a hydrophilic polymer; and, a dispensing
23 layer comprising means for dispensing the drug layer from the dosage form;
24 and wherein the process comprises formulation, the drug layer with a drug
25 possessing a particle size up to 150 microns and with a hydrophilic polymer
26 possessing a particle size up to 250 microns; which, through the cooperation
27 of the drug particles and the hydrophilic polymer particles and the dispensing
28 layer assisting the drug layer, the drug is delivered at a substantially uniform
29 rate of release from the dosage form.

1 5. The process for promoting a substantially uniform drug rate of
2 release according to Claim 4, wherein the hydrophilic polymer particle
3 cooperates with the drug particle as a pharmaceutical carrier for delivering
4 the drug from the dosage form.

5 6. The process for providing a substantially uniform drug rate of
6 release according to Claim 4, wherein the dispensing layer assists in
7 displacing the drug layer from the dosage form.

8 7. The process for providing a substantially uniform drug rate of
9 release according to Claim 4, wherein a wall encases both the drug layer
10 and the dispensing layer and comprises means for releasing the drug from
11 the dosage form.

12 8. The process for providing a substantially uniform drug rate of
13 release according to claim 4, wherein a wall surrounds the drug layer and the
14 dispensing layer, and a subcoat between the wall and the drug layer and the
15 dispensing layer, and the dosage form comprises exit means for releasing
16 the drug from the dosage form.

17 9. A dosage form for the delivery of a drug, wherein the dosage
18 form comprises:

19 (a) a composition;

20 (b) a dose of drug of less than 150 microns in the
21 composition;

22 (c) a hydrophilic polymer of less than 250 microns in the
23 composition;

24 (d) a wall comprising a composition permeable to the
25 passage of fluid that surrounds the dose of drugs and the hydrophobic
26 polymer; and

27 (e) means in the wall for delivering the drug at a substantially
28 uniform rate from the dosage form.

29

- 1 10. A dosage form for the delivery of a drug, wherein the dosage
2 form comprises
- 3 (a) a drug composition;
- 4 (b) a dose of drug of less than 150 microns in the drug
5 composition;
- 6 (c) a hydrophilic polymer of less than 250 microns in the
7 drug composition;
- 8 (d) a coat that surrounds the drug composition comprising
9 means for delaying release of drug from the drug composition;
- 10 (e) a wall comprising a composition that surrounds the coat;
11 and,
- 12 (f) means in the dosage form for delivering the drug from the
13 dosage form over time.
- 14 11. The dosage form according to Claim 10, wherein the drug is a
15 member selected from the group consisting of verapamil, nifedipine,
16 nilvadipine, flunarizine, nimodipine, diltiazem, nicardipine, nitredipine,
17 nisoldipine, felodipine, amlodipine, isradipine, cinnarizini and fendiline.
- 18 12. The dosage form according to Claim 10, wherein the drug is a
19 member selected from the group consisting of ramipril, fusinopril, altiopril,
20 benazepril, libenzapril, alacepril, cialzapril, cilazaprilat, perindopril, zofenopril,
21 inalapril, lisinopril, imidapril, spirapril, rentiapril, captopril, delapril, olindapril,
22 indalapril and quinapril.
- 23 13. A dosage form for the delivery of a drug, wherein the dosage
24 form comprises:
- 25 (a) a drug composition comprising a drug of less than
26 150 micron size and a pharmaceutically acceptable hydrophilic polymer
27 carrier of less than 250 micron size for this drug;

1 (b) a displacement composition in contact with the drug
2 composition comprising means for causing fluid to enter the displacement
3 composition whereby the displacement composition increases in volume and
4 displaces the drug composition from the dosage form;

5 (c) a wall comprising means for permitting a fluid to enter the
6 dosage form that surrounds the drug composition and the displacement
7 composition; and

8 (d) means in the wall for delivering the drug as a
9 substantially uniform rate over a dispensing time.

10 14. The dosage form for delivering the drug according to Claim 13,
11 wherein the drug is a member selected from the group consisting of a calcium
12 channel blocker and an angiotensin enzyme inhibitor.

13 15. The dosage form for delivering the drug form for delivering the
14 drug according to Claim 13, wherein this drug is a member selected from the
15 group consisting of alpha receptor blocking drugs, beta receptor blocking
16 drugs, antianginal drugs, antiarrhythmus drugs, antiembolus drugs,
17 antihypertensive drugs, digitalis drugs, hemorheologic drugs, inotropic drugs,
18 myocardial infarction prophylaxis drugs, cerebral vasodilators, coronary
19 vasodilators, peripheral vasodilators, and vasopressor drugs.

20 16. A dosage form for delivering a drug orally to a patient in need
21 of a drug, wherein the dosage form comprises:

22 (a) drug composition comprising a drug having a particle
23 size up to and including 150 microns, and a hydrophilic polymer carrier
24 having a particle size up to and including 250 microns for the drug;

25 (b) a displacement composition in contrast with the drug
26 composition and comprising a polymer that expands in the presence of fluid
27 for displacement the drug composition from the dosage form;

28 (c) a coat free of drug that surrounds the drug and the
29 displacement composition for slowing the passageway of fluid into the dosage
30 form;

1 (d) a wall that surrounds the coat and is permeable to the
2 passage of fluid; and,

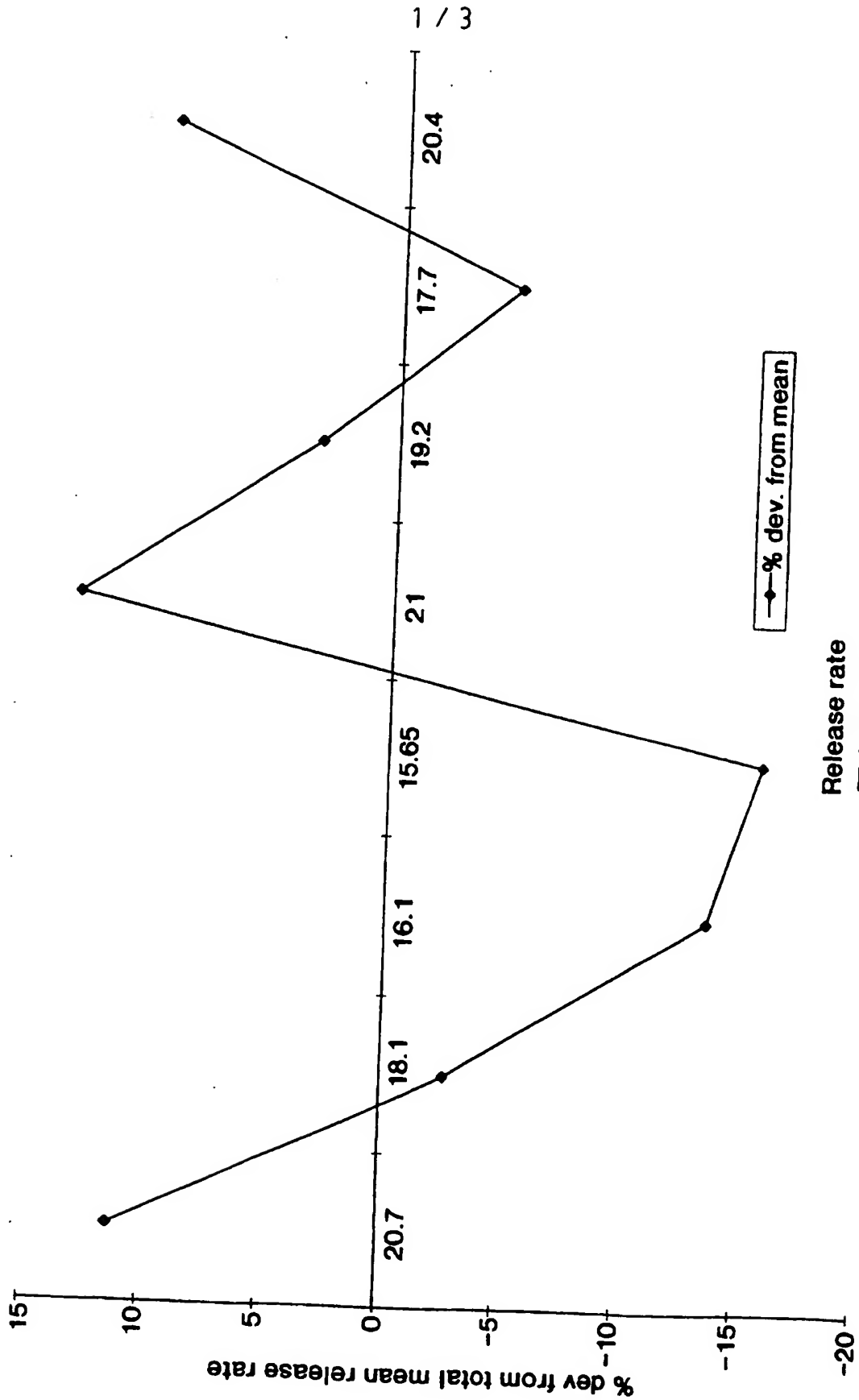
3 (e) means in the dosage form for delivering the drug from the
4 dosage form at a substantially uniform rate over time.

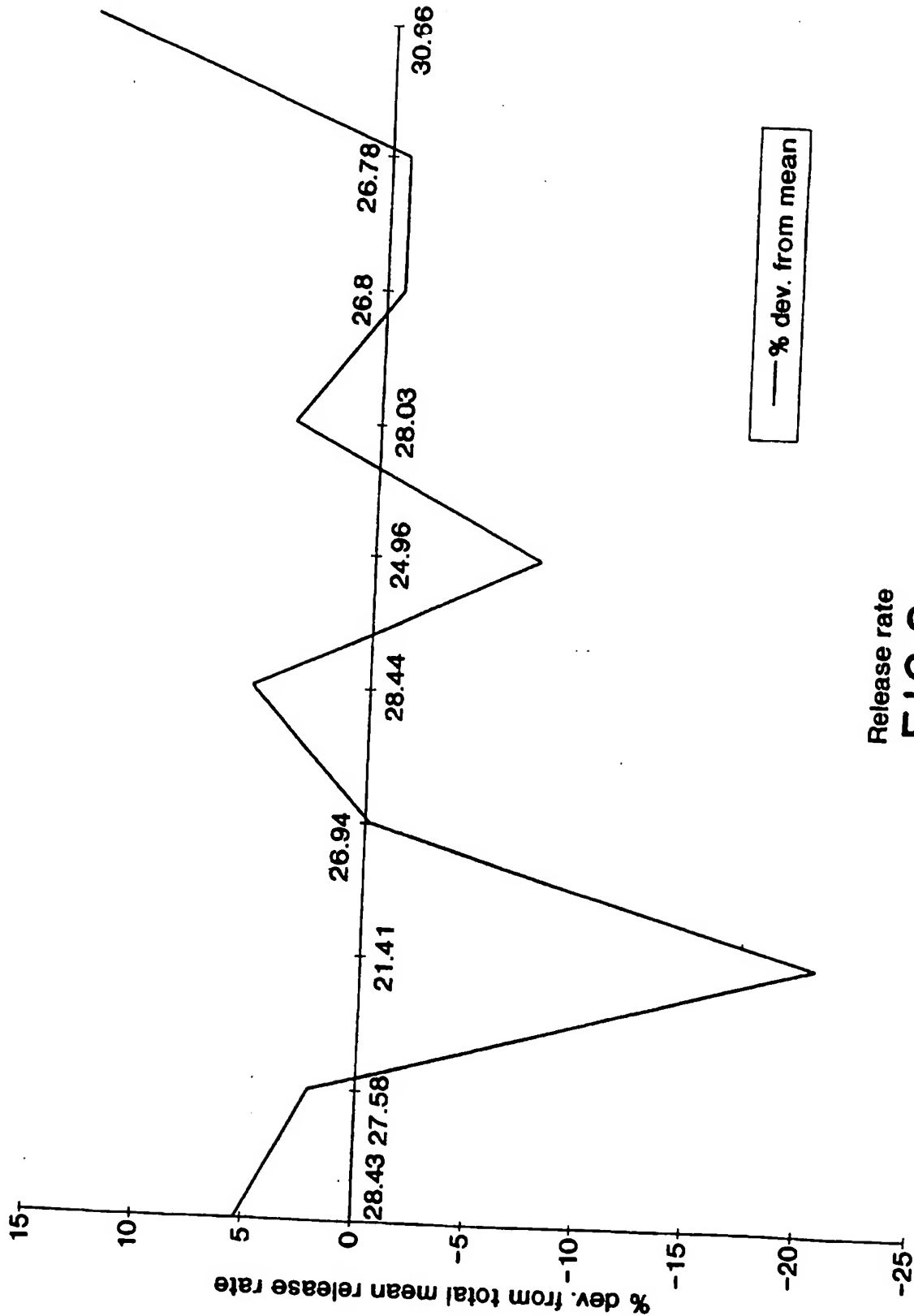
5 17. The dosage form for delivering the drug according to Claim 16,
6 wherein the drug composition comprises an antioxidant.

7 18. The dosage form for delivering the drug according to Claim 16,
8 wherein the drug composition comprises a surfactant.

9 19. The dosage form for delivering the drug according to Claim 16,
10 wherein the drug in the drug composition is a member selected from the
11 group consisting of verapamil, isradipine, nifedipine, nilvadipine, flunarizing,
12 nimodipine, diltiazem, nicardipine, nitredipine, nisoldipine, felodipine,
13 amlodipine, cinnarizine, fendiline, prazosin, clonidine, pinacidil, and alfuzosin.

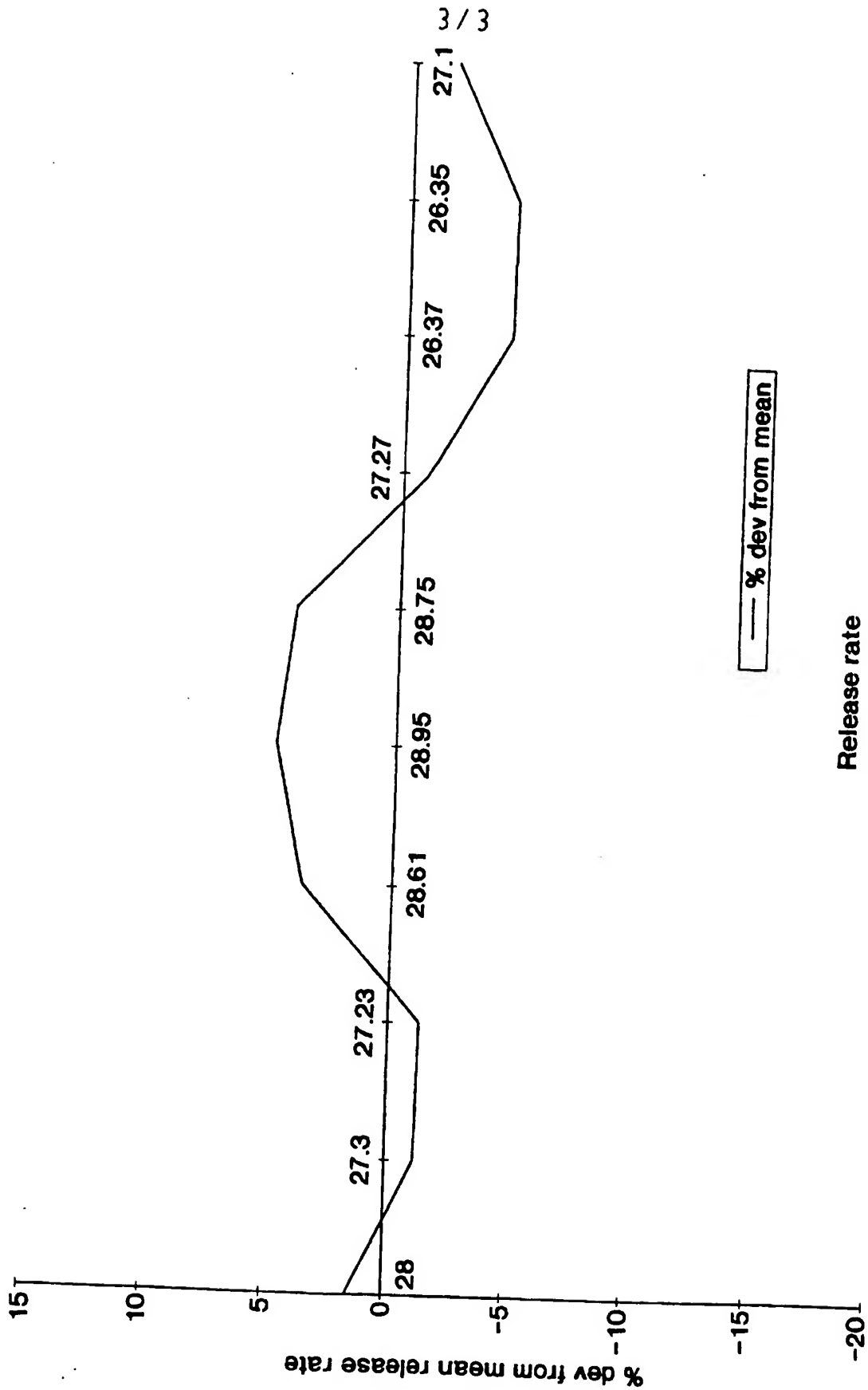
14 20. The dosage form for delivering the drug according to Claim 16,
15 wherein the drug is a member selected from the group consisting of quinapril,
16 indalapril, olindapril, delapril, captopril, rentrapril, spriapril, imidapril, lisinopril,
17 enalapril, enalaprilat, zofenopril, perindopril, cilcizaprilat, craizapril, alacepril,
18 libenzapril, benazepril, altropril, fosinopril, and ramipril.





— % dev. from mean

Release rate
FIG. 2



Release rate
FIG.3

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☒ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.